IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Martin MACPHEE *et al.*

Appl. No.: 08/474,086

Filed: June 7, 1995

For: SUPPLEMENTED AND UNSUPPLEMENTED TISSUE SEALANTS, METHODS OF THEIR PRODUCTION AND USE

AS FILED 12/16/2002

Art Unit: 1643

Examiner: M. Zeman

Atty Docket: 1327.044000C

Declaration Under 37 C.F.R. § 1.132

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

I, the undersigned, Stanley A. Friedman, declare and state that:

1. My education and professional experience are set forth on the attached copy of my résumé (Exhibit A).

2. I have read and understand the specification and claims of United States Patent Application No. 08/474,086, filed June 7, 1995 in the name of Martin MacPhee *et al.* for SUPPLEMENTED AND UNSUPPLEMENTED TISSUE SEALANTS, METHODS OF THEIR PRODUCTION AND USE.

3. As stated on my résumé, as a part of my responsibilities at the American Red Cross, I have been involved in the development of fibrin sealant matrices as a delivery system for drugs and/or biologics.

4. On July 28, 1998, I attended an interview with Examiner Zeman and Supervisory Patent Examiner Knode at the United States Patent & Trademark Office. At that

interview, Dr. Martin MacPhee, one of the inventors named in the above-identified patent application, discussed the delivery kinetics of supplemented fibrin sealant matrices.

5. In conjunction with the discussion presented by Dr. MacPhee, a series of slides were displayed at the interview. A copy of each of the slides in the series that was displayed at the interview is attached to this Declaration (Exhibit B).

Below each slide is my brief description of the content thereof and its relevance to the delivery kinetics of supplemented fibrin sealant matrices.

6. I declare further that all statements made on information and belief are believed to be true, and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and such willful false statements may jeopardize the validity of the instant patent specification or any patent issuing thereon.

Respectfully submitted,

Dr. Stanley A. Friedman

Date:

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SKGF Rev. 1/28/98 dcw

RESUME

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Work address:
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American Red Cross
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Rockville, MD 20855
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4317 Regalwood Terrace
Burtonsville, MD 20866
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EDUCATION

Doctor of Philosophy - Chemistry
University of California, San Diego
September 1976 - August 1981

Master of Science - Computer Science
Johns Hopkins University
September 1985 - July 1987

Bachelor of Arts - Chemistry
University of Maryland, Baltimore County
September 1972 - June 1976

BACKGROUND

Scientist I
Plasma Derivatives Department
American Red Cross
15601 Crabbs Branch Way
Rockville, MD 20855
October 1996 - present

Fibrin sealant forms a natural polymer matrix that makes an excellent local drug delivery system for drugs and/or biologics. My responsibilities were the development of research proposals, business plans, budgets, timelines and patents for novel uses for fibrin sealant.

Member of American Red Cross Task Force for implimentation of FDA regulations.

STANLEY A. FRIEDMAN, Ph.D.

Research Fellow
Department of Molecular Biology
American Red Cross
15601 Crabbs Branch Way
Rockville, MD 20855
Research Director - Dr. Tom Maciag
October 1990 - November 1995

Fibroblast Growth Factor (FGF) is a mitogen for cell type derived from mesodermal and neuroectodermal origins. Various *in vitro* and *in vivo* studies were performed to determine the mechanism of FGF action. These studies include the construction of FGF and FGF receptor vectors for the *in vitro* expression of these genes to elicit the secretion mechanism and signal transduction pathways of mitogenic activity and the *in vivo* expression of FGF to study the mechanism of angiogenesis. *In vivo* transfection studies to determine if a dominant-negative FGF receptor inhibits the repair processes after a balloon angioplasty.

Scientist II
Genetic Therapy, Inc.
19 Firstfield Road
Gaithersburg, Maryland
January 1989 - September 1990

Grant Awards
Small Business Innovation Research Program - Phase I - $45,023
Title - Retroviral Vectors to Express -Interferon in Human TIL

A variety of cytokine constructions were made in retroviral backgrounds for expression in humans. These retroviral particles were used to infect Tumor Infiltrating Lymphocytes (TIL) cells to enhance the TIL cells cancer fighting abilities.

Scientist Associate
Laboratory of Chromosome Biology
National Cancer Institute -
Frederick Cancer Research Facility
Frederick, Maryland
June 1984 - December 1988
Research Director - Dr. Stuart Austin

The chromosome partition of the unit-copy plasmid of the bacteriophage P1 to daughter cells of E. coli was investigated by cloning the partition region of P1 into the vector pBR322. Partition defective mutations were constructed in vitro in these clones. E. coli host mutations were also isolated and are presently being characterized. Other studies examined the regulation of the P1 partition operon by constructing protein and operon fusions to --galactosidase. Regulation defective mutations were isolated and characterized by DNA sequencing.

STANLEY A. FRIEDMAN, Ph.D.

Postdoctoral Fellow
Chemistry Department
University of Maryland, Baltimore County
September 1981 - May 1984
Research Director - Dr. John Hays

The effects of the Gam gene product on E. coli was investigated by cloning gam. The Gam gene product was found to specifically inhibit the nuclease activity of recBC in vivo and in vitro. RecBC mediated recombination, which was measured by HFr mating, P1 transduction and Chi crosses, was not inhibited by gam.

Graduate research Assistant
Chemistry Department
University of California, San Diego
September, 1976 - August, 1981
Research Director - Dr. John Leong

The mode of action of the transition metal chelating antibiotic, thioformin was investigated. The transition metals were found to stimulate cellular uptake of radioactively labeled thioformin. Attempts were made to determine the target of the antibiotic by measuring in vivo inhibition of cellular processes in the presence of the antibiotic. Some of the processes examined were ATP, ppGpp and pppGpp levels, O_2 consumption, and the synthesis of DNA, RNA, and proteins. The antibiotic induced a shift-down by effecting energy production.

Undergraduate Research Assistant
Chemistry Department
University of Maryland, Baltimore County
December, 1974 - August, 1976

The membrane bound sugar transport system of Staphylococcus aureus was examined by purification and characterization of the enzymes involved in the process. In vivo and in vitro enzyme kinetic studies were performed.

Supervision and training of a graduate student

STANLEY A. FRIEDMAN, Ph.D.

PUBLICATIONS

1. Friedman, S.A. and J.B. Hays. 1977. Initial characterization of hexose and hexitol phosphoenolpyruvate-dependent phosphotransferases of *Staphylococcus aureus*. J. Bacteriol. 130:991.

2. Friedman, S.A., R.M. Cooper, and J.B. Hays. 1977. The same reversible aggregating soluble protein is required for PEP-dependent phosphorylation of mannitol and sorbitol in *Staphylococcus aureus*. FEMS.1:311.

3. Bell, S.J., S.A. Friedman, and J. Leong. 1979. Antibiotic action of N-methylthioformohydroxamate metal complexes. Antimicrob. Agents Chemother. 15:387.

4. Hays, J.B., T.A.G. Smith, S.A. Friedman, E. Lee, and G.L. Coffman. 1984. RecF and RecBC functions during recombination of non-replicating, UV-irradiated phage DNA and during other recombination processes. Cold Spring Harbor Symp. Quant. Biol. 49:475-483.

5. Abeles, A.L., S.A. Friedman, and S.J. Austin. 1985. Partition of unit-copy miniplasmids to daughter cells III. The DNA sequence and functional organization of the P1 partition region. J. Mol. Biol. 85:261-272.

6. Friedman, S.A., and J.B. Hays. 1986. Selective inhibition of *Escherichia coli* RecBC enzyme functions by plasmid-encoded phage Gam activity. Gene. 43:255.

7. Austin, S., S. Friedman, and D. Ludtke. 1986. The partition functions of three unit-copy plasmids can stabilize the maintenance of plasmid pBR322 at low copy number. J. Bacteriol. 168:1010-1013.

8. Friedman, S., K. Martin and S. Austin. 1986. The partition system of the P1 plasmid. In:Banbury Report 24:Antibiotic Resistance Genes: Ecology, Transfer, and Expression (S.B. Levy and R.P. Novick, eds.). Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, pp. 285-295.

9. Martin, K.A., S.A. Friedman, and S.J. Austin. 1987. The partition site of the P1 plasmid. Proc. Natl. Acad. Sci., USA. 84:8544-8547.

10. Friedman, S.A., and S.J. Austin. 1988. The P1 plasmid-partition system synthesizes two essential proteins from an autoregulated operon. Plasmid 19:103-112.

11. Zhan, X., X. Hu, S. Friedman, and T. Maciag. 1992. Analysis of Endogenous and Exogenous Nuclear Translocation of Fibroblast Growth Factor-1 in NIH 3T3 Cells. Biochem. Biophys. Res. Comm. 188:982-991.

12. Jackson, A., S. Friedman, X. Zhan, K.A. Engleka, R. Forough, and T. Maciag. 1992. Heat shock induces the release of fibroblast growth factor 1 from NIH 3T3 cells. Proc. Natl. Acad. Sci. USA 89:10691-10695.

13. Forough, R., X. Zhan, M. MacPhee, S. Friedman, K.A. Engleka, T. Sayers, R.H. Wiltrout, and T. Maciag. 1993. Differential Transforming Abilities of Non-secreted and Secreted Forms of Human Fibroblast Growth Factor-1. J. Biol. Chem. 268:2960-2968.

14. Friedman, S., X. Zhan, and T. Maciag. 1994. Mutagenesis of the Nuclear Translocation Sequence in FGF-1 Alters Protein Stability But Not Mitogenic Activity. Biochem. Biophys. Res. Comm. 198:1203-1208.

15. Maciag, T., X. Zhan, S. Friedman, S. Garfinkel, I. Prudovsky, A. Jackson, J. Wessendorf, X. Hu, S. Gamble, J. Shi, S. Brown, F. Tarantini, and A. Zimrin. 1994. Novel Mechanisms of Fibroblast Growth Factor-1 Function. Prog. Hormone Res. 49:105-123.

16. Jackson, A., F. Tarantini, S. Gamble, S. Friedman, and T. Maciag. 1995. The Release of Fibroblast Growth Factor-1 from NIH 3T3 Cells in Response to Temperature Involves the Function of Cysteine Residues. J. Biol. Chem. 270:33-36.

17. Imamura, T., S. Friedman, S. Gamble, Y. Tokita, S.R. Opalenik, J.A. Thompson, and T. Maciag. 1995. Identification of the Domain Within Fibroblast Growth Factor-1 Responsible for Heparin-dependence. Biochim. Biophys. Acta 1266:124-130.

18. Finch, P.W., L.K. Yee, M.Y.W. Chu, T.M. Chen, M.H. Lipsky, T. Maciag, S. Friedman, M.H. Epstein, and P. Calabresi. 1997. Inhibition of Growth Factor Mitogenicity and Growth of Tumor Cell Xenografts by a Sulfonated Distamycin A Derivative. Pharmacology 55:269-278.

19. Shi, J., S. Friedman, and T. Maciag. 1997. A Carboxyl-Terminal Domain in Fibroblast Growth Factor (FGF)-2 Inhibits FGF-1 Release In Response to Heat Shock *In Vitro*. J. Biol. Chem. 272:1142-1147.

20. Jackson, M.R., S.A. Friedman, A.J. Carter, V. Bayer, J.R. Burge, M.J. MacPhee, W.N. Drohan, and B.M. Alving. 1997. Hemostatic Efficacy of a Fibrin-based Topical Agent in a Femoral Artery Injury Model: A Randomized, Blinded, Placebo-controlled Study. J. Vas. Surg. 26:274-280.

Patents

MacPhee, M., W.N. Drohan, D. Beall, S. Friedman, D. Tuthill, and V. Bayer. 1998. Hemostatic Sandwich Bandage. Patent Pending